Angiogenesis and its inhibition: potential new therapies in oncology and non-neoplastic diseases.

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To summarise the key points: The ability to mount an angiogenic response is probably present in all tissues, and stimulation of endothelial cells by any one of a wide variety of factors initiates a cascade of events leading to angiogenesis. In most tissues the overall lack of angiogenesis in normal situations probably results from the interaction of a complex series of multifactorial systems, each of which maintained in a state of balance between stimulation and inhibition. An imbalance in any one of these systems, for example by an increase in the concentration of a growth factor, may lead to angiogenesis. Inhibition of angiogenic stimuli is unlikely to be effective as an approach to new angiostatic drugs, given the multiple stimulatory pathways available. Tumour cells for example may induce angiogenesis via release of numerous growth factors, prostaglandins etc, and by their attraction of inflammatory cells which in turn release multiple angiogenic stimuli. Inhibitory modulation of many of the individual steps of capillary growth which occur following an angiogenic stimulus can block the angiogenic response. This leads to the expectation that an effective inhibitor of a single key step in this cascade would be able to completely suppress angiogenesis. Inappropriate angiogenesis is an important factor in many diseases including cancer and arthritis. In particular angiogenesis is an absolute requirement for neoplastic growth of solid tumours, and the establishment of secondary growths. There is also a strong link between induction of angiogenesis by a tumour and its ability to metastasise. Several drugs with proven clinical effects in diseases involving angiogenesis have recently been found to be angiogenesis inhibitors, and this may be their primary mechanism of action. In particular the activities of methotrexate and gold compounds in arthritis, and alpha-interferon and medroxyprogesterone in cancer therapy may be due to inhibition of angiogenesis. In animal models, treatment with angiogenesis inhibitors has proven anti-tumour effects in vivo, and can both reduce metastases and lead to regression of the primary growth by necrosis following capillary retraction. In man the

success of alpha-interferon and TNF alpha in AIDS related Kaposi's sarcoma may be due to inhibition of angiogenesis. Interferon has also been successfully used to treat pulmonary hemangiomatosis, in which angiogenesis in the lung may be the pathogenic basis of the disease.

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